Nomenclature of Immunoglobulins

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As the problem of biological nomenclature grows, the effective system worked out for the immunoglobulins can provide a model for the clarification of a confused situation.

THE gentle art of good name calling does not come easily to most scientists, at least in regard to the objects of their study. None the less, clear and unambiguous names are needed for described phenomena and if possible the name and the phenomenon should be logically associated. There are special problems of nomenclature in immunology which arise partly from the complexity of the immune response itself, and also from the great rate at which knowledge is acquired. The great variability of immunoglobulins has presented a major problem of nomenclature. This article is concerned chiefly with the nomenclature of immunoglobulins in man, and is intended as an introduction for non-specialists. It also indicates one way in which problems of nomenclature have been tackled on an international basis.

Although the phenomenon of antibody activity in plasma has been recognized since 1890 from the work of von Behring and Kitasato on tetanus antitoxin, the finding that antibody molecules belong to a distinguishable group of plasma proteins had to wait for the development of adequate techniques of protein analysis. In 1938 Tiselius and Kabat laid the foundation for subsequent work by showing that antibody to diphtheria toxoid in man was found in the γ-globulin electrophoretic fraction. γ-Globulin preparations, although now made by methods such as Cohn's ethanol fractionation procedure rather than electrophoresis, contain most of the antibody present in human serum. They are used therapeutically in man when the passive transfer of antibodies is required.

The idea that all antibodies were to be found in a homogeneous group of proteins did not, however, survive for long. Analysis in the ultracentrifuge, for example, showed that some antibodies were present in two molecular forms, sedimenting at different rates. The γ-globulin concept finally became outmoded by Grabar and Williams's simple and elegant technique of immunoelectrophoresis, which revealed several immunochemically distinct proteins within the γ-globulin region. These proteins were electrophoretically heterogeneous, and overlapped into the β-globulin regions.

What then was the relationship between these various proteins in the β and γ-globulin regions and antibodies? Three of the proteins which could readily be distinguished by immunoelectrophoresis were soon discovered to include molecules with antibody activity. These, according to their immunoelectrophoretic designation, were γ-globulin, β_{2A} or γ_{1A}-globulin and β_{2M} or γ_{1M}-globulin. Diversity of nomenclature had already appeared. The major protein, γ-globulin, was further designated by names such as γss (γ-sensu strictu) by a classically trained school of immunologists; and 7S γ-globulin where the orientation was perhaps more towards physicochemical concepts than towards dead languages. Moreover, β_{2M}-globulin turned out to be none other than a protein designated 19S γ-globulin on the basis of ultracentrifugal analysis.

This confusing situation was not a novel one in science. It reflected the rapid progress of the protein chemistry of γ-globulins. None the less, the diversity of names was confusing and could seriously have retarded progress in research and its application to medicine. A novel way was available to solve this problem. In 1963 the World Health Organization (WHO) established its immunology unit, charged with the responsibility of ensuring the effective development of immunology for human welfare on an international scale. The first WHO meeting on the nomenclature of human immunoglobulins took place in Prague in 1964, and WHO has subsequently sponsored a series of meetings and publications on this subject (refs. 1–5). In the publications some of the leading scientists in the field have made proposals for solving problems of nomenclature. Many of the proposals have found general acceptance, and have resulted in great simplification; an exception is the proposal concerning the nomenclature of genetic markers of immunoglobulins which has appeared less appropriate in the light of subsequent research, and is not generally accepted.

In 1964, the term "immunoglobulin" was proposed as the generic name for all types of proteins with antibody activities, and for structurally related proteins. "Immunoglobulin" thus superseded "γ-globulin". Two symbols were proposed to indicate immunoglobulin; Ig was regarded as the logical abbreviation, but the symbol "γ" was also retained in recognition of its historical association with immunoglobulins. As will be seen, although the γ nomenclature suffers from a degree of ambiguity, both Ig and γ are now well established symbols, and immunologists remain typically faithful to the symbol of their choice.

Classes and Types of Immunoglobulins

Names were also proposed in 1964 for the different classes of immunoglobulins. Clear distinction between classes is essential, for these proteins differ widely in their biological properties. The major protein in the γ-globulins was designated IgG; the macroglobulin characteristic of 19S γ-globulin (γ_{1M} etc.) was recognized in the symbol IgM, while for the previous β_{2A} or γ_{1A}-globulin, the highest common factor was indicated in IgA. In this way rational-

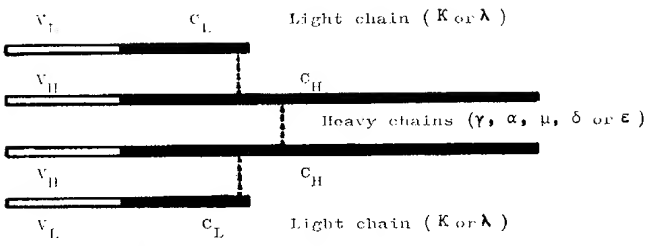

Fig. 1. A diagram of the structural unit of immunoglobulins and its constituent polypeptide chains and regions. Immunoglobulin molecules may consist of one or more of such units, for example, IgG molecules comprise one unit, IgM molecules five units. See text for a description of the symbols used for the regions.

ity was introduced while preserving a form of continuity with previous terms. The terminology provided for the introduction of names for new classes of immunoglobulins; IgD and IgE have since been added. The names of these proteins, together with their salient characteristics, are shown in Table 1.

These terms IgG, IgA and so on served to define the major classes of immunoglobulins. At the same time a terminology was established for the constituent polypeptide chains of immunoglobulin molecules. The fundamental unit of structure of immunoglobulins irrespective of their class, consists of two pairs of identical chains as shown in Fig. 1. The larger chains were designated heavy chains and the smaller chains light chains. Because differences between classes of immunoglobulins are due entirely to differences between their heavy chains, these were designated by the Greek letter corresponding to their class, for example, the heavy chains of IgG as γ-chains, the heavy chains of IgA as α-chains and so on. The light chains are common to all immunoglobulin classes but occur in two forms or types. These were designated type K or type L and the chains as κ or λ. At the time when this nomenclature was established the evidence of heterogeneity of chains was derived almost entirely from immunochemical analyses. Subsequent studies of the primary structure of immunoglobulins have shown that the differences between chains are due to major differences in primary structure.

Table 1. CLASSES OF HUMAN IMMUNOGLOBULINS

Name	Median serum concentration (mg/ml.)	Molecular weight	Biological properties
IgG (γG)	1·2	150,000	The major immunoglobulin in serum
IgA (γA)	0·4	180,000	The major immunoglobulin in secretions. Does not activate complement
IgM (γM)	0·12	900,000	"Early" antibodies often occur in this class
IgD (γD)	0·003	186,000	Function unknown
IgE (γE)	0·00025	200,000	Responsible for immediate type sensitivity

Sub-classes and Genetic Markers

Further sub-divisions of immunoglobulins are now recognized. For example, sub-classes occur in IgG, IgA and IgM. Human IgG can be divided into four sub-classes on the basis of antigenic differences between γ-chains. These are designated IgG1, IgG2, IgG3 and IgG4 in the order of their relative serum concentrations. Differences between sub-classes are due to a series of differences of amino-acid residues within heavy chains. Sub-classes are functionally distinct, for example, IgG1 and IgG3 sub-classes readily activate complement, whereas IgG_2 activates weakly and the IgG4 sub-class not at all.

Whereas all immunoglobulin sub-classes are present in all (normal) members of the species, genetic markers or allotypic specificities of immunoglobulins are present in some, but not all, individuals. In man, genetic markers have been found in γ and α-chains and in λ-chains, and allotypic specificities have also been recognized in rabbits and other animal species. Two principal series of factors have been recognized in man. Grubb, working with antiglobulins present in the serum of patients with rheumatoid arthritis, was the first to recognize one series of factors which he designated Gm. This indicated that the factor was present in gamma-globulin. More than twenty Gm factors are now recognized, usually designated by symbols such as Gm a, Gm f, although a numerical notation has been proposed[2]. Individual Gm factors are associated with individual sub-classes of IgG and Gm factors in the different sub-classes are found to be genetically closely linked. A second unrelated genetic system present in man is designated by the symbol Inv, described initially by Ropartz to be present in the serum of patient V. The factor is a property of λ chains. Inv a+ differ from Inv b+ light chains by the substitution of leucine for valine at residue 191 in the constant region of the chain (discussed later). Another variability, termed Oz, has been demonstrated at a similar position in the constant region of κ chains. Oz, however, differs from InV in that both Oz+ and Oz− κ-chains can occur in the same individual,

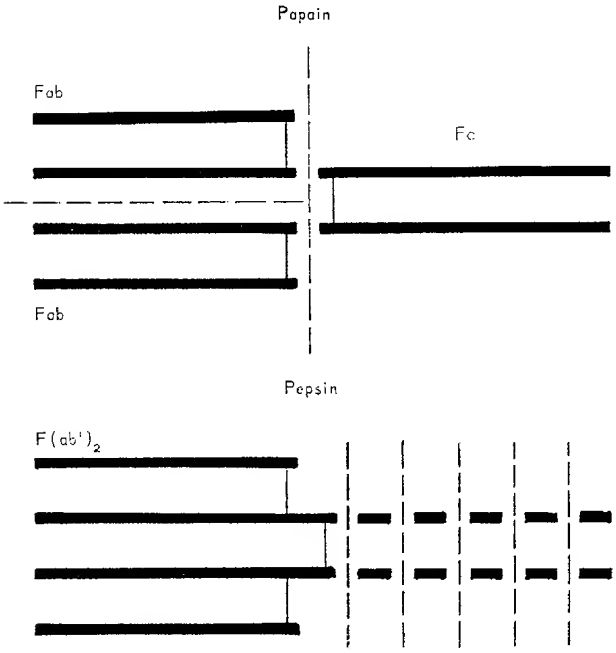

Fig. 2. The actions of papain and pepsin on IgG. Papain yields two identical Fab fragments and one Fc fragment. Pepsin yields one $F(ab')_2$ fragment, the carboxy terminal halves of the heavy chains are split into small peptides.

Enzymatic Fragments

Names have also been given to the fragments of immunoglobulins obtained by enzymatic digestion (Fig. 2). The system which has been most extensively studied is the action of papain on IgG. Three major fragments are produced and the study of these has been valuable in

elucidating the molecular structure of IgG and in assigning different functional properties to different regions of the molecule. The fragment which is composed of the carboxy terminal halves of the heavy chains is sometimes crystallizable and is designated Fc (fraction crystallizable) on this account. The two remaining fragments are identical and each comprises the amino terminal half of a heavy chain and one light chain. When obtained from antibody molecules these fragments can bind antigen, and so have been designated Fab (fragment antigen binding). That part of the heavy chain included in Fab has been designated Fd. Pepsin cleaves the heavy chains of IgG at a site slightly closer to the amino terminus, yielding one $F(ab')_2$ fragment, the remaining part of the heavy chain being further split into several smaller fragments. Most of the biological properties of IgG antibody molecules other than antibody binding are present in the Fc fragment, for example, the ability to activate complement, to attach to cells as cytophilic antibody and to be transferred across the placenta.

Constant and Variable Regions

Studies of primary structure have shown that light chains may be divided into two approximately equal regions. These are the carboxy terminal half of the chain where within a given type the sequence is invariable (except for Inv and Oz differences I have noted), and the amino terminal half of the chain where numerous differences in sequence are found, even among light chains of the same type. These two regions are therefore referred to as constant regions and variable regions. Light chain type is determined by the sequence of the constant region. Variable regions do not consist of an infinite variety of amino-acid sequences; rather a distinct group of variable regions has been found to be associated with a constant region of given type, that is, one group is found in κ-chains, and a different group in λ-chains. Further patterns of variability have been recognized within groups. On the basis of existing sequence data, three sub-groups of κ variable regions and five sub-groups of λ variable regions can be distinguished in man.

Heavy chains also have constant and variable regions. The variable regions of the heavy chains are at the amino terminal and and are of approximately the same length as the variable regions of light chains. The variable regions of heavy chains are also comparable with those of light chains in the occurrence of groups of distinctive sequence patterns. Contrary to the light chains, however, there is evidence that the groups of individual patterns may not be restricted to heavy chains of a given class, that is, the same individual pattern may occur in γ, α and μ chains. There is much indirect evidence that the antigen binding activities of immunoglobulins are determined by the primary structure of the variable regions of heavy and light chains.

The constant region of heavy chains which has been most extensively studied is that of IgG. Three linearly arranged adjacent regions have been found which have sequence similarities both to each other and to the constant region of the light chains. These three regions have been called homology regions. In addition, that region of the heavy chains close to the site of the action of papain is notably rich in proline residues and evidence derived from electron microscopy suggests that this is the most flexible region of the immunoglobulin molecule. This general region is therefore sometimes referred to as the "hinge region".

Symbols have been proposed for these different regions of immunoglobulin molecules. Constant regions of heavy and light chains are indicated by C_H and C_L respectively. Variable regions are similarly indicated as V_H and V_L. To specify a particular class or sub-class of heavy chain the symbol H could be replaced by the symbol of the chain. Thus the constant region of α-chains would be indicated by the symbol $C\alpha$. Similarly, to indicate an individual type of light chain the symbol L could be replaced by the symbol for the chain, for example, the variable region of κ chains would be indicated by V_κ. A more detailed account of proposals for the nomenclature of the regions, of half-cystinyl residues, and for formulae for immunoglobulin molecules will be found in ref. 5.

Immunoglobulins in Species other than Man

The nomenclature I have described has been developed primarily with regard to the immunoglobulins of man. Nomenclature in other species is more confused; diverse systems have grown up partly based on evidence from within a species, and partly on comparisons with other species. It would be desirable that the nomenclature which has been successfully applied to the classes and types of human immunoglobulins also be used for other species. The logical basis of such nomenclature would be the demonstration of evolutionary homology between the immunoglobulins of different species. Thus names for immunoglobulins in species close to man would be relatively easy to assign, whereas nomenclature in more distant species could prove to be more difficult.

The firmest ground for the demonstration of evolutionary homology is the finding of similarities of primary structure. Although rapid progress has been made it is hardly to be expected that this information will soon be available for many species, especially for those immunoglobulins which are difficult to isolate in purified form. In these circumstances antigenic cross reactivity forms a valuable tool for the investigation of similarities of structure, and it seems reasonable to designate immunoglobulins on this basis. Other types of comparison are on less sure ground. Criteria such as molecular weight and carbohydrate content must carry less weight than those based on primary structure.

Functional criteria could be seriously misleading. For example, it was generally considered that IgA was the major immunoglobulin of colostrum and other secretions, but in the bovine species a protein more closely related to IgG seems to be the major immunoglobulin of colostrum, whereas the protein more comparable with IgA is only a minor component.

In summary, the nomenclature of human immunoglobulins, although necessarily complex, has now been placed on a rational and generally agreed basis which is sufficiently flexible to accommodate new information. Studies of immunoglobulins in other species have important applications to the understanding of the activities of comparable proteins in man, and the establishment of homology is therefore of broader significance than its applications to questions of nomenclature. None the less, a satisfactory nomenclature for the immunoglobulins of various species can hardly be established before adequate evidence for homology is obtained.

[1] *Bull. WHO*, **30**, 447 (1964).
[2] *Bull. WHO*, **33**, 721 (1965).
[3] *Bull. WHO*, **35**, 953 (1966).
[4] *Bull. WHO*, **38**, 151 (1968).
[5] *Bull. WHO*, **41**, 975 (1969).